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The Use of Ketamine as an Antidepressant: A Narrative Literature Review

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A B S T R A C T

Ketamine is a structural analog of the dissociative anesthetic and recreational drug phencyclidine (PCP). Like phencyclidine, ketamine causes analgesia and amnesia without the cardiovascular and respiratory depression associated with general anesthesia. This review aimed to describe the use of ketamine as an antidepressant. Ketamine reverses CSP in the prefrontal cortex, hippocampus, and NAc within one day of administration via postsynaptic glutamate activation with upregulation of neurotrophic signaling and increased protein synthesis, restoring synaptic connectivity lasting for days or even weeks. The antidepressant properties of ketamine may also be due to its effect on mitochondrial energy metabolism. Ketamine as an anesthetic has been developed in clinical practice because other significant effects have been found, namely as an antidepressant. In conclusion, monitoring must be carried out in antidepressant therapy administration because ketamine has possible side effects such as hypersalivation, tachycardia, increased systemic arterial pressure, and intracranial pressure.

1. Introduction

Depression has become one of the major problems in modern society and the third cause of disability globally.[1,2] Advances in conventional antidepressant treatment only waned in a few weeks, resulting in widespread resistance to treatment. Half a century ago, many researchers began to understand the pathophysiology and psychopathology of depression better. There are many clinical laboratory studies to determine the mechanism and clinical properties of ketamine.[3,4] Ketamine is a structural analog of the dissociative anesthetic and recreational drug phencyclidine (PCP). Like phencyclidine, ketamine causes analgesia and amnesia without the cardiovascular and respiratory depression associated with general anesthesia.[5] In administration during surgery, ketamine is usually combined with a benzodiazepine to reduce the psychological symptoms that occur. Subanesthetic dosing can use for acute and chronic pain management, sedation, and treatment of major depression. Ketamine can produce an antidepressant effect, a short-term dissociative effect affecting consciousness and perception.[6] Ketamine acts on a cascade of intracellular signaling pathways that generate an inflammatory response, which is involved in the pathophysiology of depression. Depression occurs due to monoamine deficiency and increased glutamate, and its center is present at the N-methyl-D-aspartate receptor (NMDAR).[7] Ketamine has been shown to have antidepressant effects and has recently approving to treat therapeutic-resistant depression, with clear indications, contraindications, and treatment regimens. This review aimed to describe the use of ketamine as an antidepressant.

Neurobiology and antidepressant properties of ketamine

Two hypotheses are linking cortical synaptic to ketamine. Ketamine blocks NMDA on GABA interneurons, causing disinhibition of pyramidal structure-laden activity in the cortex, thereby increasing receptor signaling that triggers a cascade of pathways, including amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor activation, secretion brain-derived neurotrophic factor (BDNF), and mammalian target activation of rapamycin signaling (mTOR); NMDA receptor antagonists inhibit eukaryotic elongation factor-2 kinase and increase cortical synaptic connectivity.[8,9]

Ketamine reverses CSP in the prefrontal cortex, hippocampus, and nucleus accumbens within one day of administration via postsynaptic glutamate activation with upregulation of neurotrophic signaling and increased protein synthesis, restoring synaptic connectivity lasting for days or even weeks.[10] The antidepressant properties of ketamine may also be due to its effect on mitochondrial energy metabolism. Ketamine as an anesthetic has been developed in clinical practice because other significant effects have been found, namely as an antidepressant. The effect of ketamine as an antidepressant is related to the type of change in brain oscillations.[11] Ketamine modulates glucose metabolism in the brain, affects anxiety and depression, and effectively treats resistant depression. Physiologically, this mechanism is maintained by the supply of energy to the population of neurons. Several studies conclude that ketamine rapidly and significantly reduces suicidal tendencies and anxiety, and this effect can last for one week. Mood depression is frequently reported in postoperative patients; small doses of ketamine (0.5 mg kg^{-1}) at induction of anesthesia can reduce mood depression by increasing serum brain-derived neurotrophic factor (BDNF).[11]

Ketamine is a non-competitive NMDA receptor antagonist that causes the main antidepressant effect.[12] Then proceed with inhibition of glutamatergic input to GABA interneurons resulting in glutamatergic disinhibition, decreased feedback, and increased glutamatergic excitatory transmission. Other neurochemistry mechanisms, such as glycogen synthase kinase-3 (GSK3) and mTOR, mediate the effects of fast-acting antidepressants. Ketamine also modulates TrkB signaling, which activates BDNF via a complex cascade involving the -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR). The dopamine system is also involved in modulating the phenotypic markers of depression. It has also been found that they are potential targets in the mechanisms of fast-acting antidepressants, for example, the suicide receptor ketamine. Another component of the antidepressant effect is the eukaryotic elongation factor-2 kinase (eEF2K), which is the key to mediating the effects of fast-acting antidepressants.[13,14]

Drug monitoring should be conducted due to ketamine's side effects. Several side effects caused when giving ketamine are acute psychiatric and psychomimetic effects. The cardiovascular effects of ketamine are increased blood pressure and heart rate.[15] Ketamine has possible side effects such as hypersalivation, tachycardia, increased systemic arterial pressure, and intracranial pressure.

2. Conclusion

The antidepressant properties of ketamine may also be due to its effect on mitochondrial energy metabolism. Drug monitoring should be carried out during antidepressant therapy administration.

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